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EXAMINER	
GUNTER, DAVID R	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/402,618	Applicant(s) DONG ET AL.
	Examiner David Gunter	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *90-136* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90-136* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The examiner acknowledges the applicants claim to priority for the instant application as a continuation in part of application 08/851,588 filed 05/05/1997.

2. The examiner notes that this application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 90-106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Regarding Claims 90, 99, and 101, the phrase "target nucleic acid comprising first and second non-contiguous single-stranded regions separated by an intervening region comprising a double stranded region" is confusing. It is unclear whether the double stranded region of the intervening region is double stranded due to binding of the region to a complementary strand of nucleic acid such as a primer or due to the formation of secondary structure such as a hairpin structure. It is suggested that the structure of the intervening region, particularly the double stranded region of the intervening region, be clearly explained.

b. Regarding Claim 90, 99, 101, 104, and 105, the phrase "capable of binding" is unclear. "Capable of" is not an active method step, and may be interpreted to recite either a property of the oligonucleotides or a potential method of using the oligonucleotides. The claim should be amended to state that the oligonucleotides are complementary to the target nucleic acid and hybridize to the target nucleic acid.

c. Regarding Claim 90, it is not readily apparent from the claim how the combination of the nucleic acid target, oligonucleotide probes, and cleavage agent result in the cleavage of the bridging oligonucleotide or the second oligonucleotide. The claim should be amended to define the nature of the interactions among the nucleic acid target and the oligonucleotides including the manner in which it is determined which of the oligonucleotides is cleaved.

d. Regarding Claim 93, the term "altered" is unclear because the nature and magnitude of the alterations made to the polymerase are not specified, nor is clear how the alterations relate to the method of Claim 90. The nature of the alterations must be defined or the word "altered" removed from the claim.

e. Regarding Claims 93 and 121, the phrase "derived from" is unclear because it is not defined in the specification. The phrase should be replaced with the word "of."

f. Regarding Claim 95-97, the term "define a region of overlap" lacks antecedent basis in Claim 90. Claim 90 does not describe the nature of the interactions among the target nucleic acid and the oligonucleotides. It is suggested to recite the structure of the overlapping polynucleotides and to recite the relationship of the overlap with the method of Claim 90.

g. Regarding Claim 101, the phrase "conditions such that said bridging oligonucleotide is modified to produce a modified oligonucleotide" lacks antecedent basis. The claim does not specifically recite that the polymerase or ligase of step (iii) cause the modification of step (b), nor do they identify the nature of the modification of the oligonucleotides. Although these limitations are discussed in the specification and in Claims 102 and 103, they may not be read from the specification into Claim 101.

h. Regarding Claims 101 and 103, it is not clear from the Claims how the bridging oligonucleotide is to be modified by a ligase. The structure of the complex formed by a target nucleic acid and a bridging oligonucleotide is not adequately defined, nor is it clear to what polynucleotide the bridging oligonucleotide will be ligated.

4. Claims 109 and 110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The relevance of the 3' terminal nucleotide not complementary to the target nucleic acid is unclear. The nature of the cleavage structure of Claim 107 is not described in such a way as to make the function of the single non-complementary nucleotide evident.

5. Claims 111, 113, and 114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims lack antecedent basis in Claim 107. Claim 107

does not recite the presence of a label necessary for the detection methods of Claims 111, 113, or 114.

6. Claim 123 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The claim does not adequately describe the nature of the interactions between the two single stranded nucleic acids, the interactions among the non-target cleavage product and the two single stranded nucleic acids, or the structure of the complex formed by these nucleic acid fragments.

b. The term "exposing" is not an active method step. It is suggested that the term "exposing" should be replaced with "hybridizing"

c. The nature of the binding of the protein to the oligonucleotide complex is not adequately described. It is unclear to which portion of the complex the protein binds, and whether this portion is single or double stranded.

d. The "protein" of step (a) (iii) lacks antecedent basis in step (a) (ii) because it is not specifically recited as the DNA binding protein that binds to the protein binding region of step (a) (ii). In addition, it is suggested that the protein be defined as binding to either single-stranded or double-stranded DNA. Substituting the phrase "double-stranded DNA binding protein" for "protein" is recommended.

e. Step (b) lacks antecedent basis because it is not clearly recited how the hybridization of step (b) results in "detecting the cleavage of said cleavage structure" as

recited in the preamble. It is suggested that the claim be amended to recite the manner in which hybridization results in detection.

7. Claim 124 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "nucleic acid producing protein" is unclear. If the protein as claimed is a polymerase, it should be identified as such in the accepted terminology of the art.

8. Claim 127 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "exposing" is not an active method step and should be replaced with "hybridizing." Furthermore, step (d) lacks antecedent basis because it is not clearly recited how the hybridization of step (d) results in "detecting the cleavage of said cleavage structure" as recited in the preamble. It is suggested that the claim be amended to recite the manner in which hybridization results in detection as recited in Claim 128.

9. Claim 136 recites the limitation "providing a third oligonucleotide complementary to a third portion of said target nucleic acid ... wherein said third oligonucleotide is mixed with said reaction mixture in step b)." There is insufficient antecedent basis for this limitation in the claim. The relevance and function of the third oligonucleotide is not readily apparent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 107-136 are rejected under 35 U.S.C. 103(a) as being unpatentable over USPN 6,372,427 (hereinafter referred to as "USPN '427") in view of USPN 5,451,503 (hereinafter referred to as "USPN '503") in further view of USPN 5,635,352 (hereinafter referred to as USPN '352) in further view of Cole, et al, Analytical Biochemistry 231:309-314, 1995 (hereinafter referred to as "Cole") in further view of Guatelli, et al, Proc. Natl. Acad. Sci. USA 87:1874-1878, 1990 (hereinafter referred to as "Guatelli"). Claim 107 recites a method comprising providing (i) a cleavage agent; (ii) Hepatitis C virus target nucleic acid, said target nucleic acid comprising a first region and a second region, said second region downstream of and contiguous to said first region; (iii) a first oligonuclotide wherein at least a portion is complementary to the first portion of the target nucleic acid; and (iv) a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to the second portion of the first target nucleic acid. The components are mixed under conditions such that at least a portion of the first oligonucleotide is annealed to the first target region and wherein at least the 5' portion of the second oligonucleotide is annealed to the second region of the target so as to create a cleavage structure. The cleavage structure is cleaved to generate a non-target cleavage product which is then detected.

USPN '427 discloses a method similar to that of the instant application providing a target nucleic acid comprising "tandem, non-overlapping regions of a target single-stranded nucleic acid" (Column 1, lines 53-54). It is further disclosed that the "tandem regions of the target nucleic acid target ... are separated by 0 to 3 bases" (Column 1, lines 61-62). Tandem, non-overlapping regions separated by 0 bases anticipate the nucleic acid target recited in Claim 107 of the instant application as comprising a "target nucleic acid comprising a first region and a second region, said second region downstream of and contiguous to said region."

USPN '427 further discloses a pair of oligonucleotides, each oligonucleotide comprising a region complementary to one of the contiguous target regions (Column 1, lines 49-54). The oligonucleotides also contain regions complementary to one another, such that when the two oligonucleotides are combined with the target oligonucleotide the result is "a ternary complex" wherein a portion of the first oligonucleotide is annealed to the first target region, a portion of the second oligonucleotide is annealed to the second target region, and portions of the oligonucleotides which do not anneal to the target anneal to one another to form a double stranded, non-target oligonucleotide structure (Figure 1B).

USPN '427 further discloses that the formation of the above structure by the target nucleic acid and oligonucleotides can serve as the basis for detection of virus particles. Column 13, lines 3-8 state that the structure "may be used to detect the presence of the nucleic acids of a particular viron or bacteria in cell cultures, for example, by labeling the oligonucleotide ... or some other art recognized detection method." USPN '427 does not specifically disclose the use of a cleavage agent or detection of the cleavage of the cleavage structure. USPN '503 teaches the formation of a structure identical to that of USPN '427 and the instant application comprising

two oligonucleotides and a target nucleic acid. Figure 15A of USPN '503 (as explained in Column 21, lines 10-42) teaches that the sequence of the two oligonucleotide probes can be designed such that formation of the target nucleic acid / oligonucleotide structure results in the formation of a double-stranded non-target region containing a recognition site for a restriction endonuclease. Cleavage of the non-target region of the annealed oligonucleotides generates a non-target cleavage product which "can be detected using gel electrophoresis or other separation techniques" (Column 21, lines 15-17). It would have been obvious to one of ordinary skill in the art at the time the application was filed to combine the structure-based virus detection assay of USPN '427 with the formation of binding site for a cleavage agent as taught in USPN '503 to allow a simple means for the detection of the oligonucleotide / target nucleic acid structure.

Although the references cited above disclose that the use of a first and second oligonucleotide complementary to two adjacent, contiguous target regions of a nucleic acid molecule is an effective means of detecting viral nucleic acids, they do not specifically teach the use of the method to detect Hepatitis C virus (HCV). However, it would have been obvious to one of ordinary skill in the art at the time the application was filed to adapt the method for the detection of HCV nucleic acid based on the known ability of the method to detect a broad range of RNA and DNA viruses (USPN '427 Column 2, lines 15-17) and the known importance of HCV as a major human pathogen in order to derive a rapid and sensitive assay for the detection of HCV infection.

a. Regarding claim 108, USPN '503 teaches the embodiment in which detecting the cleavage of the cleavage structure comprises detecting the non-target cleavage product (Column 21, lines 15-17).

b. Regarding claim 109, USPN '427 teaches the embodiment in which the 3' portion of the second oligonucleotide is not complementary to the target nucleic acid (Column 4, lines 41-47).

c. Regarding claim 110, USPN '427 teaches a variety of embodiments in which the length of the non-target regions of the oligonucleotides range from three to seven nucleotides. USPN '427 teaches that shorter regions of overlap between the two oligonucleotide probes improve the accuracy of the detection method by reducing the formation of oligonucleotide dimers in the absence of target nucleic acid (Column 9, line 64 – Column 10, line 55). It would have been obvious to one of ordinary skill in the art at the time the application was filed to reduce the degree of overlap between the oligonucleotides to the shortest possible length (a single base) in order to maximize the specificity of the detection method.

d. Regarding claims 111-114 wherein the method of detecting the cleavage of the cleavage structure comprises detection of fluorescence (Claim 111), detection of mass (Claim 112), detection of fluorescence energy transfer (Claim 113), or a detection method selected from the group consisting of detection of radioactivity, luminescence, phosphorescence, fluorescence polarization, and charge (Claim 114), USPN '503 teaches the embodiments in which the oligonucleotides are labeled with a chemiluminescent label (Column 7, line 1), and a radioactive isotope (Column 21, line 21). The methods listed in USPN '503 and those listed in Claims 111-114 are known to those of ordinary skill in the art to be art-equivalent means of detecting polynucleotides, and therefore it would have been obvious to substitute one manner of detection for another.

e. Regarding claims 115-116 wherein the first (Claim 115) or second (Claim 116) oligonucleotide is attached to a solid support, none of the references cited thus far teach the attachment of the oligonucleotide primers to a solid support. USPN '352 teaches a method for performing solid-phase hybridization assays using a pair of oligonucleotide primers wherein the sequence of the oligonucleotides are complementary to "distinct but proximate segments" of a nucleic acid target (Column 13, lines 47-49). One or both of the pair of primers is/are attached by one end to a solid support (Figures 8 and 16). USPN '352 teaches that the solid-phase hybridization technique disclosed can "in principle make background undetectable, permitting the use of stronger signal amplification to increase sensitivity." USPN '352 does not teach the use of a cleavage agent, detection of the cleavage of a non-target sequence, or the use of HCV as the nucleic acid target. However, it would have been obvious to one of ordinary skill in the art at the time that the application was filed to combine the assay method of USPN '427, incorporating the use of a binding site for a cleavage agent as taught in USPN '503, with the solid-phase hybridization assay of USPN '352 to reduce background and improve the sensitivity of the assay. It would have been further obvious to use the combined assay to detect HCV based on the known ability of the method of USPN '427 to detect a broad range of RNA and DNA viruses (USPN '427 Column 2, lines 15-17) and the known importance of HCV as a major human pathogen in order to derive a rapid and sensitive assay for the detection of HCV infection.

f. Regarding claim 117, USPN '503 teaches the embodiment in which the cleavage agent is a structure-specific nuclease.

g. Regarding Claim 118, wherein the structure-specific nuclease comprises a thermostable structure-specific nuclease, the specification defines a thermostable enzyme as one that is "functional or active (i.e. can perform catalysis) at an elevated temperature, i.e. at about 55°C or higher" (page 72, lines 1-3). Restriction enzymes that satisfy this definition of thermostable are well known in the art. It would have been obvious to combine the method of USPN '503 with the use of a thermostable enzyme in order to allow the cleavage reaction to be carried out at a higher temperature. High temperatures favor specific binding of the oligonucleotides to their targets and would minimize false-positive results which may occur when the oligonucleotides hybridize in a non-specific manner at low temperature.

h. Regarding Claims 119-122 wherein the cleavage agent comprises a 5' nuclease (Claim 119), a thermostable 5' nuclease (Claim 120), a thermostable 5' nuclease comprising a portion of the amino acid sequence of a thermostable DNA polymerase derived from a thermostable organism (Claim 121) selected from the group containing *Thermus aquaticus*, *Thermus flavus*, and *Thermus thermophilus* (Claim 122): USPN '503 teaches the embodiment in which the cleavage agent is S1 nuclease, which comprises 5' nuclease activity (Claim 119 of the instant application; USPN '503 Column 2, lines 30-33). USPN '503 does not specifically teach the use of a thermostable 5' nuclease. The specification defines a thermostable enzyme as one that is "functional or active (i.e. can perform catalysis) at an elevated temperature, i.e. at about 55°C or higher" (page 72, lines 1-3). 5' nucleases that satisfy this definition of thermostable are well known in the art. It would have been obvious to combine the method of USPN '503 with the use of a

thermostable enzyme in order to allow the cleavage reaction to be carried out at a higher temperature. High temperatures favor specific binding of the oligonucleotides to their targets and would minimize false-positive results which may occur when the oligonucleotides hybridize in a non-specific manner at low temperature. Thermsostable DNA polymerases, including those derived from bacteria of the genus *Thermus* are well known in the art, and are further known to possess 5' nuclease activity. It would have been obvious to select a thermostable DNA polymerase derived from a bacterium of the genus *Thermus* because of its known stability at high temperature and its ready commercial availability.

i. Regarding Claims 123-126, USPN '503 teaches the embodiment in which the annealed oligonucleotides create "a biologically or chemically significant site which may be distant from the target nucleic acid yet is formed only in the presence of the nucleic acid" (Claim 123 of the instant application; USPN '503 Column 4, lines 22-25) and teaches "a site which can be acted upon by a T7 RNA polymerase" as an example of such a site (Claims 124-126 of the instant application; USPN '503 Column 4, lines 38-39 and lines 53-58.).

j. Regarding Claim 127, none of the literature thus far cited teaches the specific embodiment wherein detection of the cleavage product is based on production of a RNA polymerase binding region by the extension of the cleavage product using a DNA polymerase. Cole teaches a method for the detection of the cleavage of a cleavage structure wherein the cleavage products hybridize to a single stranded nucleic acid and act as primers for replication of the single stranded nucleic acid by a DNA polymerase to

form a double stranded RNA polymerase binding region. The influenza virus endonuclease cuts small (10-13 base) fragments from mRNA molecules of the host cell, which are then used as primers to allow transcription of the viral genome (Cole, page 309, left column, first paragraph). Cole teaches the use of a synthetic nucleic acid template that is capable of binding the nucleic acid fragments generated by the influenza virus endonuclease. T7 DNA polymerase is then used to synthesize the complement to the synthetic nucleic acid template using the cleavage products as primers. Cole teaches that the advantages to this polymerase-based assay technique for the cleaved nucleotides include high throughput, the ability to monitor the activity of the nuclease directly, and high sensitivity (page 309, right column, third paragraph).

Cole does not specifically teach the use of template-dependent RNA polymerase to generate RNA transcripts. However, Guatelli teaches a method of DNA replication identical to the method of the instant application using RNA and DNA polymerases. Guatelli teaches that the "accumulation of both target nucleic acid specific RNA and cDNA has been observed, quantitated, and characterized" (page 1874, left column, first paragraph). As described above, it would have been obvious to one of ordinary skill in the art at the time the application was filed to combine the nucleic acid detection technique of USPN '427 with the formation of a binding site for a sequence-specific nuclease as disclosed in USPN '503 to form a cleavage structure and a non-target cleavage product. Furthermore, it would have been obvious to one of ordinary skill in the art to detect the formation of the non-target cleavage product using the method of Cole in order to allow sensitive and specific detection of the cleavage product. It would have

been still further obvious to amplify the newly transcribed DNA of the method of Cole using the enzyme based system of Guatelli, or other art recognized equivalents such as PCR, in order to further increase the sensitivity of the assay.

k. Regarding Claim 128, Guatelli teaches the embodiment in which the RNA transcripts are detected (page 1874, left column, first paragraph).

l. Regarding Claim 129, Guatelli teaches the embodiment in which the template dependent RNA polymerase is T7 RNA polymerase (page 1874, right column, second paragraph).

m. Regarding Claim 130-132, Cole teaches the embodiment in which the target nucleic acid is rendered single stranded by heating the target (page 311, "scheme 1").

n. Regarding Claim 133-134, Cole teaches the embodiment in which $MgCl_2$ is added to the reaction mixture (page 310, left column, last paragraph).

o. Regarding Claim 135, wherein the first and second oligonucleotides are provided in excess concentration compared to the target nucleic acid, providing the oligonucleotide primers in excess of the target DNA is a known practice in the art to ensure that scarcity of the oligonucleotides does not limit the reaction being carried out. It would have been obvious to one of ordinary skill in the art to provide the oligonucleotides in excess concentration compared to the target nucleic acid.

p. Regarding claim 136, USPN '503 teaches the embodiment in which a third oligonucleotide complementary to a third portion of the target nucleic acid anneals upstream of the first oligonucleotide (Figure 9E).

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 90-98 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,194,149 (hereinafter referred to as UPSN '149). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 90 of the instant application recites a method in which a target nucleic acid comprising at least a portion of Hepatitis C virus nucleic acid is

combined with a first and second oligonucleotide in the presence of a cleavage agent under conditions such that either the first or second oligonucleotide is cleaved.

Claim 1 of UPSN '149 recites a method nearly identical to that of Claim 90 of the instant application in which two oligonucleotides are combined with a target nucleic acid under conditions such that one of the two oligonucleotides is cleaved. Claim 1 of UPSN '149 does not specifically recite that the target nucleotide sequence comprises at least a portion of Hepatitis C virus (HCV) nucleic acid. However, the specification of USPN '149 discloses that "it is intended that the present invention encompass methods for the detection of RNA-containing virus, including, but not limited to ... flaviviruses (e.g., hepatitis C virus)" (Column 18, line 62 – Column 19, line 2). Examples 8 and 9 of USPN '149 demonstrate the analysis of the folded structure of HCV (Column 60, beginning at line 45, and Column 62, beginning at line 60). The specification of USPN '149 further discloses that HCV is the predominant cause of post-transfusion non-A, non-B hepatitis, and is the major cause of chronic liver disease world-wide (Column 46, lines 43-47). Because HCV was known to be compatible with the method of USPN '149 as shown in Examples 8 and 9, and because HCV was further known to be a major human pathogen, it would have been obvious to one of ordinary skill in the art at the time the instant application was submitted to apply the method of USPN '149 to a target molecule containing HCV nucleic acid to allow detection of HCV.

a. Regarding Claims 91-93, USPN '149 recites the embodiments wherein the cleavage agent (Claim 90 of the instant application; Claim 1 of USPN '149) comprises a nuclease (Claim 91 of the instant application; Claim 2 of USPN '149), a thermostable 5' nuclease (Claim 92 of the instant application; Claim 3 of USPN '149), and a thermostable

5' nuclease comprising an altered polymerase derived from a native polymerase of *Thermus* species (Claim 93 of the instant application; Claim 4 of USPN '149).

b. Regarding Claim 94, USPN '149 discloses the embodiment wherein the nuclease of Claim 91 of the instant application is *Archaeoglobus fulgidus* FEN-1 endonuclease (Column 71, line 7).

c. Regarding Claims 95-97, USPN '149 recites the embodiments wherein the conditions of mixing the target nucleic acid with the oligonucleotides allow for hybridization so as to define a region of overlap of the oligonucleotides (Claim 95 of the instant application; Claim 5 of USPN '149), wherein the overlap comprises one base (Claim 96 of the instant application; Claim 6 of USPN '149) or more than one base (Claim 97 of the instant application; Claim 7 of USPN '149).

d. Regarding Claim 98, USPN '149 discloses the embodiment wherein the method is used as "an analysis for the identification of HCV types," (Column 33, line 50-51) which are as listed as HCV subtypes 1a, 1b, 2a/c, and 3a (Column 54, line 22).

12. Claims 99-100 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 of USPN 6,355,437 (hereinafter referred to as USPN '437). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 99 of the instant application recites a method comprising (a) providing (i) a target nucleic acid comprising first and second non-contiguous single-stranded regions separated by an intervening region, said intervening region comprising two double-stranded regions separated by a single-stranded region, wherein said target nucleic acid

comprises at least a portion of Hepatitis C virus (HCV) nucleic acid and (ii) a bridging oligonucleotide capable of binding to said first and second non-contiguous single-stranded regions; and (b) mixing the target nucleic acid and oligonucleotide under conditions such that the oligonucleotide hybridizes to the target to form an oligonucleotide/target complex.

Claim 1 of UPSN '437 recites a method nearly identical to that of Claim 99 of the instant application in which a target nucleic acid has two non-contiguous single-stranded regions separated by an intervening region comprising two double-stranded regions separated by a single-stranded region. Claim 1 of USPN '437 further recites mixing the target nucleic acid with a bridging oligonucleotide capable of binding to the first and second non-contiguous single stranded regions under conditions such that the oligonucleotide hybridizes to the target to form an oligonucleotide/target complex. Claim 1 of UPSN '437 does not specifically recite that the target nucleotide sequence comprises at least a portion of Hepatitis C virus (HCV) nucleic acid. However, the specification of USPN '437 discloses that "it is intended that the present invention encompass methods for the detection of RNA-containing virus, including, but not limited to ... flaviviruses (e.g., hepatitis C virus)" (Column 19, line 67 – Column 20, line 7). Examples 8 and 9 of USPN '437 demonstrate the analysis of the folded structure of HCV (Column 60, beginning at line 45, and Column 62, beginning at line 60). The specification of USPN '437 further discloses that HCV is the predominant cause of post-transfusion non-A, non-B hepatitis, and is the major cause of chronic liver disease world-wide (Column 46, lines 43-47). Because HCV was known to be compatible with the method of USPN '437 as shown in Examples 8 and 9, and because HCV was further known to be a major human pathogen, it would have been obvious to one of ordinary skill in the art at the time the instant application was submitted to apply the

method of USPN '437 to a target molecule containing HCV nucleic acid to allow detection of HCV.

a. Regarding Claim 100, USPN '437 discloses the embodiment wherein the method is used as "an analysis for the identification of HCV types," (Column 33, line 52-53) which are as listed as HCV subtypes 1a, 1b, 2a/c, and 3a (Column 54, line 22).

13. Claims 101-106 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 of USPN '437 in view of USPN '149. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 101 of the instant application recites a method comprising (a) providing (i) target nucleic acid comprising first and second non-contiguous single stranded regions separated by an intervening region comprising a double-stranded portion, wherein said target nucleic acid comprises at least a portion of HCV nucleic acid; (ii) a bridging oligonucleotide capable of binding to said first and second non-contiguous single-stranded regions; and (iii) a reactant selected from the group consisting of polymerases and ligases; and (b) mixing said target nucleic acid, said bridging oligonucleotide and said reactant under conditions such that said bridging oligonucleotide is modified to produce a modified oligonucleotide.

Claim 1 of UPSN '437 recites a method nearly identical to that of Claim 99 of the instant application in which a target nucleic acid has two non-contiguous single-stranded regions separated by an intervening region comprising two double-stranded regions separated by a single-stranded region. Claim 1 of USPN '437 further recites mixing the target nucleic acid with

a bridging oligonucleotide capable of binding to the first and second non-contiguous single stranded regions under conditions such that the oligonucleotide hybridizes to the target to form an oligonucleotide/target complex. Claim 1 of UPSN '437 does not specifically recite that the target nucleotide sequence comprises at least a portion of Hepatitis C virus (HCV) nucleic acid. However, the specification of USPN '437 discloses that "it is intended that the present invention encompass methods for the detection of RNA-containing virus, including, but not limited to ... flaviviruses (e.g., hepatitis C virus)" (Column 19, line 67 – Column 20, line 7). Examples 8 and 9 of USPN '437 demonstrate the analysis of the folded structure of HCV (Column 60, beginning at line 45, and Column 62, beginning at line 60). The specification of USPN '437 further discloses that HCV is the predominant cause of post-transfusion non-A, non-B hepatitis, and is the major cause of chronic liver disease world-wide (Column 46, lines 43-47). Because HCV was known to be compatible with the method of USPN '437 as shown in Examples 8 and 9, and because HCV was further known to be a major human pathogen, it would have been obvious to one of ordinary skill in the art at the time the instant application was submitted to apply the method of USPN '437 to a target molecule containing HCV nucleic acid to allow detection of HCV.

Claim 1 of USPN '437 does not recite combining the nucleic acid target and bridging oligonucleotide with a polymerase or ligase under conditions such that the bridging oligonucleotide is modified. USPN '149 teaches the emodiment in which a target nucleic acid comprising first and second non-contiguous single-stranded regions separated by an intervening region comprising a double stranded portion is mixed with a bridging oligonucleotide and a reactant selected from the group consisting of polymerases and ligases under conditions such that

the bridging oligonucleotide is modified (Column 18, lines 6-16). It would have been obvious to one of ordinary skill in the art at the time the application was filed to combine the nucleic acid target / oligonucleotide complex of USPN '437 with the detection method of USPN '149 to allow rapid and sensitive detection of the formation of the target / oligonucleotide complex.

a. Regarding Claim 102, USPN '149 teaches the embodiment in which the reactant is a polymerase and the modified oligonucleotide comprises an extended oligonucleotide (Column 18, lines 6-16).

b. Regarding Claim 103, USPN '149 teaches the embodiment in which the reactant is a ligase, and the modified oligonucleotide comprises a ligated oligonucleotide (Column 18, lines 6-16).

c. Regarding Claim 104, USPN '149 teaches the embodiment in which the bridging oligonucleotide is capable of binding to fewer than ten nucleotides of each of the first and second non-contiguous regions (Column 18, lines 28-31).

d. Regarding Claim 105, the instant application recites the further limitation to claim 101 that the bridging oligonucleotide is capable of binding seven or fewer nucleotides of each of the first and second non-contiguous single stranded regions. USPN '149 teaches the embodiment in which the bridging oligonucleotide is capable of binding to eight or fewer nucleotides of each of the first and second non-contiguous single stranded regions (Column 18, lines 28-31). USPN '149 does not specifically teach that the bridging oligonucleotide binds seven or fewer nucleotides from each non-contiguous single stranded region, however the teaching "eight or fewer" oligonucleotides of USPN '149 embraces "seven or fewer" oligonucleotides as recited in the instant application.

e. Regarding Claim 100, USPN '437 discloses the embodiment wherein the method is used as "an analysis for the identification of HCV types," (Column 33, line 52-53) which are as listed as HCV subtypes 1a, 1b, 2a/c, and 3a (Column 54, line 22).

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David R. Gunter whose telephone number is (703) 308-1701. The examiner can normally be reached on 9:00 - 5:00 M - F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-9212 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.

David R. Gunter, DVM PhD
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